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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/162,648	09/29/98	HISERODT	J

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HM12/1024

EXAMINER	
STROUP,C	
ART UNIT	**PAPER NUMBER**
1633	2

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/162,648	Hiserodt JC
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☒ Responsive to communication(s) filed on *Jun 20, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment Paper 9, filed 6/20/00, has been entered. Claims 10, 16, 19, and 20 have been amended. Claims 1-20 are currently pending in the present application.

It is noted that the Official Action, Paper 11, ~~filed~~ mailed 9/29/00, has been voided so that a new art rejection may be applied.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-10, 12-16, and 18-20 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Granger (US Patent 5,837,233).

Applicant's claimed invention is to a method for treating cancer or eliciting an anti-cancer response in a human patient suffering from melanoma, pancreatic, liver, colon, prostate, or breast cancer, and a pharmaceutical composition, comprising implanting at or around the tumor site a first cell population containing alloactivate lymphocytes that are allogeneic to leukocytes in the patient and comprising about $2*10^9$-$2*10^{10}$ donor PBMC and $1*10^8$-$2*10^9$ patient or 2nd donor PMBC's, wherein said implantation is repeated within an interval of at least three

days, one to eight weeks, or two to twelve months (claims 1, 7, 8, 11, 12, 18). Said cell populations are obtained by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes for a period of about 48-72 hours, or are obtained by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes and harvested at about the time of initial alloactivation, via acridine orange or CD69 assay (claims 11, 17). The first implantation stimulates a response, such as an inflammatory or immunological response, against the tumor prior to the second implantation, and wherein said lymphocytes are activated against leukocytes of the patient or of a third-party donor (claims 2-6). Said methods also include a pharmaceutical composition comprising alloactivated lymphocytes allogeneic to leukocytes in a cancer patient packaged with written information for the treatment of the patient (claims 19, 20).

Granger et al teach a method for treating cancer, such as melanoma, pancreatic, liver, colon, prostate, and breast cancer (claim 37), in a human patient comprising implanting at or around the site of a tumor a cell population of about $2*10^9$-$6*10^9$ cells and comprising alloactivated human donor lymphocytes produced by coculturing said lymphocytes *ex vivo* with leukocytes from said patient at a ratio of 10:1 to 20:1 donor: patient cell ratio, for at least 48 hours, and preferrably 1-5 days (claim 37; col 7, lines 30-50). Treatment results in the patient generating a therapeutic or immunologic response against tumor growth and transplanted lymphocytes up to 74 weeks post implant (col 4, lines 1-35; claims 1-37). Granger et al also teach the use of a pharmaceutical composition comprising a sterile vial containing a unit dosage of mixed lymphocyte culture (a mixture of live alloactivated donor and patient lymphocytes) and bearing a label which sets forth information concerning the pharmaceutical use of the composition in treating a tumor in a human (col 6, lines 8-16).

Applicants state in Paper 9, filed 6/20/00, page 7, that Granger et al teach away from administering two doses because two patients showed progressive reduction in tumor mass over periods of 58 and 74 weeks, respectively. The Office is at a loss as to comprehending how the successful response of two patients to one dose dissuades the artisan

from administering a second dose to patients experiencing a relapse or a plateau in tumor reduction. It is a common practice within the cancer therapy field that when the efficacy of a treatment begins to subside, then another treatment or dose is administered (See Fleshner et al, Cell Transplantation, 1992, 1: 307-312). Therefore, based on this common therapeutic practice and the disclosure of Granger which does not specifically state to administer only one dose, and which the Applicant states in Paper 9, filed 6/20/00, page 6, is equivalent to the Applicant's claimed method with the exception that the Applicant is claiming two doses be administered, then one of skill in the art would administer a second dose of alloactivated lymphocytes to the tumor site to prolong the efficacy and potency of the anti-tumor therapy.

It is noted that the Applicant's arguments in Paper 9, filed 6/20/00, page 10, stating that the specification discloses an unanticipated syngeristic effect from the use of sequential administrations of alloactivated lymphocytes (specification, pg 11-12) has been found to not be persuasive in light of data from Granger (US Patent 5,837,233) and the declaration by Dr. T. Gatanaga. Granger et al teach that the longevity of patients receiving one administration varies from approximately 140 days to 350 days (see Figure 1), whereas Gatanaga et al teach that the administration of two doses of allogeneic cells provides approximately the same range. Additionally, Gatanaga et al fails to provide a statistical analysis comparing the longevity of patients receiving one dose versus those receiving two. In light of these facts, the Applicant has not demonstrated in a human model that an unanticipated synergistic effect occurs upon administering two or more doses of alloactivated lymphocytes. If on the other hand, the Applicant is relying upon the animal model of Figure 3 and 4 to support the synergistic effect, than the Applicant must specifically state that the animal model correlates with what would be expected to result in humans, which would result in the pending application being anticipated by other animal models (e.g. Kruse et al).

3. Claims 1-9, and 13-15 are rejected under 35 U.S.C. 102(b) as anticipated by Kruse et al (Proc Natl Acad Sci, 1990, IDS-reference 20) and (FASEB J, 1996, IDS-reference 21).

Kruse et al teach a method of treating rats bearing 9L glioscarcoma (*Proc Natl Acad Sci*, 1990, IDS-reference 20) and humans for recurrent malignant glioma (FASEB J, 1996, IDS-reference 21) by intracranial implantation into a tumor of allogeneic lymphocytes stimulated in vitro by co-culturing for 4-5 days with normal lymphocytes derived from a syngeneic rat (1990) or by co-culturing for 2-3 weeks with allogeneic donor lymphocytes (1996), wherein multiple doses were administered in both experiments. For example, the rats received three injections (day 0, 7, and 14), and the human patients received from 1-5 implantations given every other month, wherein results demonstrated a substantial reduction in tumor size. Therefore, the claimed invention was clearly anticipated.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granger, GA (US Patent 5,837,233) as applied to claims 1-10, 12-16, and 18-20 above; and further in view of Feldhaus et al (US Patent 5,759,805) and Haugland, RP (1992).

Applicant's claimed invention further comprises the process wherein donor lymphocytes are alloactivated by coculturing ex vivo with stimulator leukocytes and harvested at about the time of initial alloactivation, measurable with acridine orange or CD69 assay.

Haugland RP teach that acridine orange is a fluorescent dye utilized for assessing cell functions, such as metabolic processes (pg 172-173).

Jung et al teach that CD69 is an antigen on human lymphocytes expresed during the early stages of cell activation(abstract).

In light of Granger GA, Jung et al, and Haugland, it would have been obvious to one of ordinary skill in the art to determine the point of initial alloactivation via acridine orange or CD69 assays because they were routine in the art in studying cellular metabolic processes (Haugland, pg 173) and that CD69 expression is specific to early stage activated lymphocytes (Jung et al, abstract).

No claim is currently allowed.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at (703) 308-0447. The fax number for this Group is (703) 308-0294.

Carrie Stroup